

Remarks

In the Office Action mailed October 6, 2004, claims 105-140 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 105-125 and 127-140 were rejected under 35 U.S.C. § 103(a) as obvious over US Pat. No. 5,395,825 - ("Feinberg"), in view of *Lea et al.*, *Nocera et al.*, *Clark et al.*, *Thomas et al.*, *Thaler et al.*, and *Prakash et al.* Claims 113 and 114 were rejected as obvious over Feinberg, in view of *Lea et al.*, *Nocera et al.*, *Clark et al.*, *Thomas et al.*, *Thaler et al.*, and *Prakash et al.*, *Harlow et al.*, and *Martin-Villa et al.* Claim 126 was rejected as obvious over Feinberg, in view of *Lea et al.*, *Nocera et al.*, *Clark et al.*, *Thomas et al.*, *Thaler et al.*, *Prakash et al.*, and *Grainger et al.*, and claim 133 was rejected as obvious over Feinberg, in view of *Lea et al.*, *Nocera et al.*, *Clark et al.*, *Thomas et al.*, *Thaler et al.*, *Prakash et al.*, and *Heidenreich et al.* The specific grounds for rejection, and applicant's response thereto, are set out in detail below.

Claims 105 to 134 are pending in the instant application. Claim 105 has been amended and claims 135 to 140 have been canceled. Applicants submit that the amendments to claim 105 are fully supported by the specification. Consideration of the amended claims is requested in view of the following comments.

Rejection under § 112, first paragraph

Claims 105-140 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner alleges that the specification does not enable claims purportedly treatment of any and all infertility condition including miscarriage, spontaneous abortion, preeclampsia, early embryonic loss and implantation failure by exposing a female to an MHC class I antigen on leukocytes and TGF β . Applicants respectfully traverse.

Applicant prior response explained in detail why the instant disclosure fully enables treatment of a variety of conditions, including spontaneous abortion, preeclampsia, early embryonic loss and implantation failure, by exposing a mucosal surface of a prospective mother to TGF β and a MHC Class I antigen present on leukocytes or in seminal plasma of the prospective father, where the antigen is

capable of eliciting a Th-1 response Applicants reiterate that the methods disclosed in the specification are enabling for these treatments but, without acquiescing in the propriety of the rejection and solely to expedite the progress of this application towards allowance, applicants have amended claim 105 so that it conforms to the invention that the Examiner concedes is fully enabled. Specifically, the amended claim replaces the term "fertility" with "recurrent miscarriage" and the term "MHC class I antigen" has been amended to recite "MHC class I antigen on the sperm."

Applicants submit that the amended claims conform to the invention that the Examiner concedes is fully enabled and, accordingly, withdrawal of the rejection respectfully is requested.

Rejection under § 103(a)

Claims 105-125 and 127-140 are alleged obvious over US Pat. No. 5,395,825 - ("Feinberg"), in view of Lea *et al.*, Nocera *et al.*, Clark *et al.*, Thomas *et al.*, Thaler *et al.*, and Prakash *et al.* and claims 113 and 114 under 35 U.S.C. § 103(a) as being unpatentable over Feinberg, in view of Lea *et al.*, Nocera *et al.*, Clark *et al.*, Thomas *et al.*, Thaler *et al.*, and Prakash *et al.*, Harlow *et al.*, and Martin-Villa *et al.* The Examiner has also rejected claim 126 under 35 U.S.C. § 103(a) as being unpatentable over Feinberg, in view of Lea *et al.*, Nocera *et al.*, Clark *et al.*, Thomas *et al.*, Thaler *et al.*, and Prakash *et al.*, and Grainger *et al.* and claim 133 as being unpatentable over Feinberg, in view of Lea *et al.*, Nocera *et al.*, Clark *et al.*, Thomas *et al.*, Thaler *et al.*, and Prakash *et al.*, and Heidenreich *et al.*

The Examiner asserts that Feinberg differs from the claimed invention "only in that the method of treating infertility by inducing immune tolerance by exposing [a] mucosal surface of [the] prospective mother with semen or MHC class I antigen of a prospective father capable of eliciting a Th-1 response[,] and substantially purified TGFβ." However, the Examiner alleges that the claimed invention would have been obvious in view of new combinations of art cited. Applicants respectfully traverse.

All claims are presumed initially to be non-obvious. A *prima facie* case of obviousness requires three elements: (1) a teaching or suggestion of all of the claim

limitations; (2) a suggestion or motivation to modify or combine the teachings of the applied prior art; and (3) a reasonable expectation of success in reaching the claimed invention. The Examiner bears the initial burden of supporting any *prima facie* assertion of obviousness with adequate facts. MPEP § 2142 (Feb. 2000). Applicants respectfully submit that the cited references fail to meet this test and, accordingly, respectfully submit that the rejection should be withdrawn.

Feinberg

The Examiner asserts that Feinberg differs from the claimed invention only in that the method of treating infertility by the induction of immune tolerance by exposing a mucosal surface of the prospective mother to semen or MHC class I antigen of a prospective father, which is capable of eliciting a Th-1 response, and substantially purified TGF β .

Applicants reiterate that the primary reference, Feinberg, neither teaches nor suggests the instantly claimed invention. Specifically, nowhere in Feinberg is there a suggestion of a method of treating recurrent miscarriage by inducing specific immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance. Indeed, Feinberg completely fails to teach or suggest methods of inducing immune tolerance of paternal antigens in a female.

Rather, one of ordinary skill in the art would recognize that Feinberg is concerned with the development of methods for achieving improved methods of assisted implantation of an *in vitro* fertilized conceptus. See, for example, the Abstract and claim 1:

1. A method of increasing the success rate of assisted implantation comprising administering transforming growth factor β to an ovum or conceptus prior to introduction of said ovum or conceptus into the reproductive tract of a female mammal."

The scant data provided by Feinberg are exclusively *in vitro* directed to the effects of TGF β on expression of tropho-uteronection (TUN) in trophoblasts and a purported increase in adhesion of the trophoblast to a fibronectin substrate. Feinberg clearly states that the alleged invention is directed to diagnosis and improvement of

competence of a conceptus towards uterine implantation. See for example, column 5, lines 19-24:

In accordance with the invention methods are provided for determining the competence of a conceptus toward uterine implantation comprising administering transforming growth factor β to the conceptus and evaluating the level of production by the conceptus of trophoblast fibronectin.

Not only is Feinberg concerned solely with developing methods for achieving improved implantation, but Feinberg also fails to teach or suggest any method of inducing immune tolerance in a mammalian prospective mother lacking the immune tolerance. Indeed, Feinberg contains no suggestion whatsoever that immune tolerance may be a factor in recurrent miscarriage, and certainly fails to teach or suggest that immune tolerance can be induced by the instantly claimed methods. In sum, Feinberg does not teach or suggest a method of inducting an immune tolerance in a mammalian prospective mother lacking such immune tolerance, much less in an amount effective to achieve such ends.

None of the secondary references, in any combination, fail to remedy the deficiencies of the Feinberg patent. Specifically, nowhere in Lea *et al.*, Nocera *et al.*, Clark *et al.*, Thomas *et al.*, Thaler *et al.* or Prakash *et al.* is there a teaching or suggestion for a method of treating infertility by the induction of immune tolerance by exposing a mucosal surface of the prospective mother to semen or MHC class I antigen from sperm of a prospective father, which is capable of eliciting a Th-1 response, and substantially purified TGF β . Absent this teaching by a single or combination of references, the Feinberg patent remains unobvious art.

Dependent claims 113, 114, 126 and 133 all depend from independent claim 105, which is nonobvious for the reasons set forth above and, accordingly, also are nonobvious.

Finally, applicants note that, at the time that the invention was made, the state of the prior art actually *taught away* from the invention. Specifically, one of ordinary skill in the art would have been expected that administering TGF- β to a prospective

mother, either before or after attempted conception, would *cause* miscarriage. The following articles support this concept:

- (1) Michel *et al.*, 1990, Br. J. Obstet. Gynaecol., 97(11):984-8 [Exhibit A, attached],
- (2) Graham *et al.*, 1994, Exp. Cell Research, 214:93-99 [Exhibit B, attached],
and
- (3) Graham & Lala, 1992 - Biochem. Cell Biol., 70:867-874 Exhibit C, attached].

In sum, the Feinberg patent fails to teach or suggest the presently claimed invention, and none of the cited references, either alone or in combination, disclose or suggest the specific features of Applicants' claimed invention. Accordingly, withdrawal of the rejection respectfully is requested.

CONCLUSION

In view of the above remarks and amendments, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

If any additional fees are required for the filing of this paper, Applicants authorizes the Commissioner to charge any deficiency to Deposit Account No. 08-1641.

Respectfully submitted,

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